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Letter

Complete response to an anti-programmed cell death 1 antibody following a combination therapy of an anti-programmed cell death ligand 1 antibody and a tyrosine kinase inhibitor for metastatic renal cell carcinoma

Dear Editor,

Several Phase 3 trials have demonstrated the efficacy of immune checkpoint inhibitor (ICI)-based combination therapies in the treatment of advanced clear cell renal cell carcinoma (RCC) [1–5]. However, there is still no well-defined adequate treatment for patients who experience disease progression after initial ICI-based combination therapy. In ICI-based combination therapy arms of these trials, 20.8%–54.9% of patients received subsequent anticancer drugs, most commonly receptor tyrosine kinase inhibitors such as cabozantinib and sunitinib. Only a small number of cases were treated with subsequent ICIs including nivolumab and atezolizumab [1–5]. Here, we present a case of a patient with metastatic RCC who showed a complete response to an anti-programmed cell death 1 (PD-1) antibody as ICI rechallenge after disease progression following a combination therapy of an anti-programmed cell death ligand 1 (PD-L1) antibody and a tyrosine kinase inhibitor. Written informed consent was obtained from the patient for treatment and publication of this case.

A 51-year-old Japanese man with no relevant medical or family history presented with an incidental right renal tumor and multiple lung metastases. A contrast-enhanced computed tomography (CT) scan revealed a 9.8 cm enhancing tumor in the right kidney, extending into the inferior vena cava below the diaphragm and lung metastases (T3bN0M1). Based on the International Metastatic Renal Cell Carcinoma Database Consortium prognostic model, the patient was classified as having intermediate-risk carcinoma due to the presence of two adverse factors: time of less than 1 year from diagnosis to treatment and a hemoglobin level of 12 g/dL, which was less than the lower limit of the normal range (13.7 g/dL). The patient underwent radical nephrectomy with embolectomy. The pathological diagnosis was clear cell RCC (tumor size 12 cm, pT3bN0, and Fuhrman Grade 3) (Fig. 1A). Immunohistochemical staining was 5% and 3% positive for PD-L1 and programmed cell death ligand 2 (PD-L2), respectively (Fig. 1B and C).

He was treated with combination therapy of avelumab (Merck, Darmstadt, Germany), an anti-PD-L1 monoclonal antibody, and axitinib (Pfizer, New York, USA). Avelumab was administered at a dose of 10 mg/kg every 2 weeks and axitinib was administered orally at a starting dose of 5 mg twice daily on a continuous dosing schedule. Two months after therapy initiation, CT imaging revealed a partial response (PR). However, 6 months after therapy initiation, CT imaging revealed a new brain metastasis. He then underwent stereotactic radiation therapy with a total dose of 33 Gy in three fractions, followed by axitinib monotherapy at the same dose.

After 12 months of the axitinib treatment, he had a new lung metastatic lesion. Nivolumab (Ono Pharmaceutical, Osaka, Japan) was administrated at a dose of 250 mg every 2 weeks. The patient showed a complete response to nivolumab, with the disappearance of all pulmonary metastases. The treatment was well-tolerated by the patient, with no significant adverse effects. At the last follow-up at 18 months from the initiation of nivolumab, the patient was still on this treatment.

At present, there is little evidence to support ICI rechallenges, especially after an ICI-based combination therapy. However, two small retrospective studies demonstrated the efficacy of ICI rechallenge in metastatic RCC (mRCC). In a first study, among the 45 patients with mRCC who received nivolumab plus ipilimumab combination therapy after at least one prior PD-1 axis therapy, 20% and 16% of patients showed a PR and stable disease (SD), respectively [6]. Another retrospective study evaluated the outcomes of ICI monotherapy or ICI combination therapy in 68 patients with mRCC who received prior monotherapy or combination therapy with ICI. The results revealed that 23% of patients showed a PR and 41% showed a SD. In the second study, 17 cases received anti-PD-L1-based regimen followed by anti-PD-1 monotherapy

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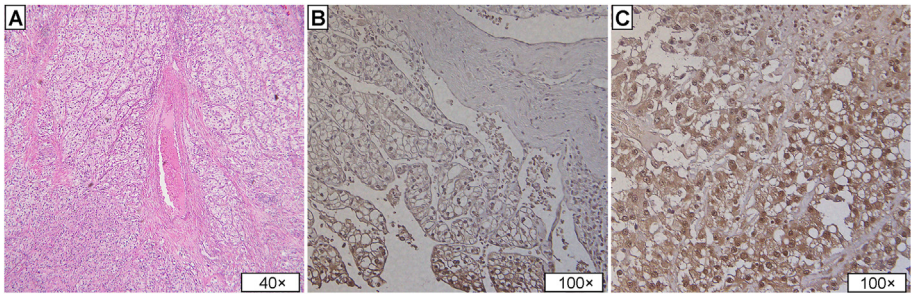

Figure 1 Pathological findings of the primary kidney tumor specimen. (A) Hematoxylin and eosin staining showing clear cell renal cell carcinoma with clear cytoplasm and a compact nested pattern. (B) Immunohistochemical staining showing that 5% of cells were stained with anti-PD-L1 (#13684, Cell Signaling Technology, Danvers, USA). (C) Immunohistochemical staining showing that 3% of cells were stained with anti-PD-L2 (#13684, Cell Signaling Technology, Danvers, USA).

as in the present case. The best objective response was PR in four patients (24%), SD in seven (41%), and progressive disease in five (29%) [7]. To the best of our knowledge, our case report is the first case in which a complete response was achieved with ICI rechallenge for mRCC. In addition, the rate of Grade 3 or 4 immune-related adverse events was 16% after ICI rechallenge and 26% after initial ICI treatments, and there were no Grade 5 events [7]. Thus, ICI rechallenge is an acceptable option for mRCC after disease progression on ICI-based combination therapies.

Anti-PD-1 (nivolumab and pembrolizumab) and anti-PD-L1 (avelumab and atezolizumab) monoclonal antibodies (mAbs) are known to block the interaction between PD-1 and PD-L1 and restore anti-tumor immune response by T lymphocytes [8]. Pembrolizumab showed a higher binding affinity to PD-1, as compared with nivolumab. Likewise, avelumab showed the highest binding affinity in anti-PD-L1 mAbs [8]. However, the impact of these affinity differences on the treatment outcome of these mAbs is not well understood. In addition, the difference of classes of PD-1 and PD-L1 mAbs on the anti-tumor effect is also unclear. In this case, the presence of PD-L2 antigen expression may explain the difference in efficacy other than the affinity of the various mAbs.

The PD-1 receptor has two ligands: PD-L1 and PD-L2. The PD-L1 is expressed in T and B cell lymphocytes, whereas the PD-L2 is mainly expressed in antigen-presenting cells [9]. The PD-L1 expression is associated with poor prognosis in various solid tumors [8]. Therefore, the oncological significance of PD-L2 expression is less well-known. In a colon adenocarcinoma mice model, it was observed that an anti-PD-L1 monoclonal antibody was partially effective, whereas an anti-PD-L2 mAb did not induce any tumor rejection. However, in mice treated with both anti-PD-L1 and anti-PD-L2 mAbs, tumor growth was suppressed completely [10]. The above data suggest that PD-L2 expression supports the anti-tumor effect of the anti-PD-L1 antibody. Therefore, we hypothesized that PD-L2 is involved in conferring resistance against PD-L1 inhibition in the present case. Furthermore, even if PD-L2-expressing cancer cells become resistant to prior anti-PD-L1 antibody treatment, anti-PD-1 antibodies may block PD-1 axis.

Author contributions

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Critical revision of the manuscript: Norihiko Tsuchiya.

Conflicts of interest

Norihiko Tsuchiya received honorarium from Merk and research fund from Ono Pharma, Osaka, Japan. The others declare no conflict of interest.

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